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Opportunistic Muscle Measurements on Staging Chest CT for Extremity and Truncal Soft Tissue Sarcoma are Associated with Survival

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Abstract

BACKGROUND AND OBJECTIVES: CT measurements of sarcopenia have been proposed as biomarkers associated with outcomes in various cancers and have typically been evaluated at the L3 vertebral level. However, staging imaging for patients with extremity and truncal soft tissue sarcoma (STS) often only includes chest CT imaging which precludes evaluation at L3. Therefore, we sought to evaluate muscle metrics at T12 on standard staging chest CT scans and evaluate for correlation with overall and event-free survival in patients with STS.

METHODS: CT Chest imaging for 89 patients with intermediate and high-grade STS (53 M, 36 F; 58.5±19.0 years old, follow up 37.4±27.1 months) was reviewed on PACS at T12 for skeletal muscle density (SMD) and skeletal muscle index (SMI).

RESULTS: Overall survival increased with increased SMD on univariate (HR = 0.61 [0.43, 0.86]) and age-adjusted analysis (HR = 0.65 [0.42, 0.89]). Event-free survival also increased with increased SMD in univariate analyses (HR = 0.68 [0.49, 0.95]) but did not maintain significance

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

after adjusting for age (HR = 0.68 [0.43, 1.07]). SMI was not a predictor of overall or event-free survival.

CONCLUSIONS: Higher SMD measured on routinely obtained staging chest CTs in STS patients are associated with improved survival.

Keywords

sarcoma; sarcopenia; myosteosis; muscle metrics

INTRODUCTION

Sarcopenia, as defined by proposed CT biomarkers, has been associated with poor prognosis in many forms of cancers including hepatocellular carcinoma, non-small cell lung carcinoma, renal cell carcinoma, esophageal carcinoma, breast carcinoma, bladder carcinoma, melanomas, and lymphomas [1–9]. In these patients, sarcopenia has been associated with multiple endpoints, including treatment failure, chemotherapy toxicity, and earlier tumor progression [10]. Clinically, sarcopenia is defined by the degenerative loss of skeletal muscle mass and function associated with aging and/or disease [10]. The most common imaging method for diagnosing sarcopenia in patients with cancer is computed tomography (CT), which allows objective measurements for assessment of muscle mass and adiposity [10]. Muscle adiposity, as an indicator of muscle quality, is measured using skeletal muscle density (SMD) whereas muscle mass, as an indicator of muscle quantity, is measured using skeletal muscle index (SMI) [6].

Due to its impact on various cancer types, Wilson et. al hypothesized that muscle mass would also affect overall survival in soft tissue sarcoma (STS) [11]. Wilson et. al assessed skeletal muscle mass using SMI at the L3 vertebral level [11]. Recently, Hendrickson et. al similarly evaluated the association of SMI on mortality in both soft tissue and primary bone tumors [12]. However, the CT protocols for staging of extremity STS often do not image at the L3 level used in those studies [7, 10–12]. Moreover, there is limited data on SMI and SMD on pelvis and abdomen CTs in patients with soft tissue sarcoma [13–14]. Due to the proclivity for lung metastases, the staging and surveillance of STS primarily includes chest CT imaging, which includes the T12 vertebral level, while routine surveillance CT of the abdomen and pelvis is less common [15–16]. Although less often investigated than at the L3 level, muscle metrics at the T12 level have also been validated in assessment of outcomes in patients with other forms of cancer besides STS [17–19]. Direct comparisons of muscle metrics measured at T12 versus L3 yield similar results in patients undergoing thoracic endovascular aortic repair, with agreement assessed yielding nearly perfect Cohen κ values (>0.85) [20]. Our study aims to analyze both muscle quantity (i.e., SMI) and quality (i.e., SMD) at the T12 vertebral level on staging chest CTs and determine their association with overall survival and event-free survival in patients with grade 2 or 3 extremity and trunk STS undergoing surgical resection.

MATERIALS AND METHODS

Prior to initiation of the study, all procedures were reviewed and approved by the IRB of the University of California, Davis. From an initial 388 patients collected based on CPT codes for surgical resection for sarcoma of the extremities, pelvis, and trunk, demographic information, physical exam findings, laboratory results, imaging, operative reports, and pathology were retrospectively extracted from patients' electronic medical records. In particular, we collected age, sex (M or F), ethnicity (white or other), Charlson-Deyo score (0 or >0), date of diagnosis, date of surgery, date of chest CT, date of locoregional or distant recurrence, date of last follow up, disease status at last follow-up (Alive with Disease (AWD), Died of Disease (DOD), or No Evidence of Disease (NED)), neo-adjuvant or adjuvant treatment status, tumor location (extremity or trunk), tumor size (≤ 10 cm or >10 cm), tumor grade (1, 2, or 3 according to the French Federation of Cancer Centers (FNCLCC)), tumor stage (II, IIIA, IIIB, or IV according to AJCC 8th ed.), surgical margins (negative or positive), as well as muscle metrics from CT images.

Patients with non-STs as well as grade 1 STs were excluded given the decreased proclivity for systemic disease. Patients who did not have a pre-operative baseline staging CT scan within 120 days prior to resection available for review were also excluded. For patients with multiple pre-operative CT scans, the CT scans closest to date of diagnosis was chosen except for two that did not capture the T12 interval.

89 patients (average age at diagnosis 58.5 ± 19.0 years with 59.6% male) were included in this single institution, retrospective review of patients diagnosed with grade 2 or 3 extremity and truncal STs between 2004–2017 for overall survival as shown in Figure 1. For event-free survival, where an event is defined as local or distant disease recurrence after surgical resection, ten patients with stage IV disease by the time of surgical resection were not included. This exclusion left 79 patients of whom 41 had NED at last follow up and 38 had DOD or had a disease recurrence either locally or distally.

Muscle metrics were calculated by manually outlining the paravertebral muscles at T12 for SMD (measured in Hounsfield units, HU) and cross-sectional area (measured in cm^2) as shown in Figure 2. Left and right paravertebral muscles were averaged in each patient. Muscle adiposity was evaluated based on CT density of the skeletal muscle, where lower SMD (HU) represents greater fat content within the muscle. Values were adjusted by -4.6 HU for CTs performed with intravenous contrast [21]. SMI (cm^2/m^2) was determined by adjusting the muscle area for patient height in meters squared, similar to BMI. Two common types of viewing software were used to make CT measurements, both the enterprise-wide PACS (which allows any viewer to make measurements) and OsiriX (which allows for semi-automated analysis of muscle). Images on PACS were analyzed by a single trained reader (R1) and images on OsiriX were analyzed by a different trained reader (R2). Both readers were blinded to patient clinical status and outcomes.

All 89 patients' vertebral levels were assessed for consensus between the two readers. 20% of images were measured twice by each reader to obtain intra-reader reliability. Average muscle metrics was calculated across both sides of the patient using each reader's first

observation for use as predictors in survival analysis. Observations from the two readers were not combined because they used different measuring software.

The effect of age on overall and event-free survival was evaluated with proportional hazard models. Log-rank tests were used to evaluate the association between overall and event-free survival with the following patient characteristics: sex (M vs. F), ethnicity (white vs. other), Charlson-Deyo score (0 vs. >0), tumor location (trunk vs. extremity), tumor size (≤10 cm vs. >10 cm), tumor grade (2 vs. 3), AJCC 8th ed. stage (II, IIIA, IIIB, or IV), and surgical margins (0 vs. 1). Proportional hazard models were used to evaluate the effect of each muscle metric on overall and event-free survival univariately and then with age as a covariate. Due to the relatively small number of events which decreased even further for some categories of patient characteristics, no additional covariates were included in the modeling. Age was centered at 0 and scaled to a standard deviation of 1. Survival modeling was conducted separately using each reader's muscle measurements. For the statistical analysis, SMD was centered at 0 and scaled to a standard deviation of 1. SMI was similarly centered and scaled within sex to remove sex differences. Kaplan-Meier plots for overall survival and event-free survival were plotted for each muscle metric stratified into three groups based on standard deviations by standardized (Z) scores: $Z \leq -1$, $-1 < Z < 1$, $Z \geq 1$. Intra-reader reliability was estimated with the intraclass class correlation assuming fixed assessors and random subjects. All statistical analyses were two-tailed at a significance level of 0.05 and performed using R Statistical Computing Software Version 3.6.1.

RESULTS

Table I summarizes patients' pre-operative and disease characteristics as well as CT muscle metrics by the following classifications: AWD, DOD, NED.

Overall Survival

Two-year and five-year overall survival was 69% [95% CI, 59% – 80%] and 54% [95% CI, 42–68] respectively for the entire cohort. Overall survival was associated with stage ($p = 0.008$). (Table II). Sex, race, Charlson-Deyo, location, grade, tumor size and margins were not significantly associated with survival (Table II).

In univariate analyses of the effects of muscle metrics, overall survival was significantly related to SMD for both readers (HR 0.61 [0.43, 0.86]) with increased survival associated with increased SMD (Table III). This relationship persisted after adjusting for age (HR 0.65 [0.42, 0.98] on PACS and HR 0.64 [0.42, 0.98] on OsiriX) (Table III). For SMI, however, there was insufficient evidence to reject the null hypothesis of no association with overall survival with or without adjusting for age for either reader (Table III). The risk of death generally increased with increasing age (HR = 1.02 [1.00, 1.04]) although this did not reach statistical significance.

Figure 3 shows Kaplan-Meier curves for each reader and muscle metric. Consistent with the proportional hazard modeling, KM curves demonstrated overall survival was greatest for patients with higher values ($Z \geq 1$) one standard deviation or greater above the mean for SMD but with no apparent relationship for SMI (Figure 3). At 2 years, overall survival was

27%, 69.6%, and 100%, for SMD one standard deviation or less below the mean, SMD within a standard deviation of the mean, and SMD one standard deviation or higher above the mean respectively. Similarly, overall survival 5 years showed a progressive relationship of increasing survival: 27%, 52.5%, and 83.3%, with higher standardized deviations of SMD.

Event-Free Survival

Like overall survival, event-free survival was also significantly associated with tumor stage (Table II). Although the estimated hazard of death or recurrence generally increased with age (HR = 1.01 [0.99, 1.03]), this did not reach statistical significance.

In univariate analyses, event-free survival increased with SMD for both observers (Table IV). When age was included the estimated effect of SMD remained similar, but the confidence intervals widened encompassing a hazard ratio of 1.0. Thus, a potential independent effect of SMD on event-free survival after adjusting for age could not be determined. Event-free survival was not significantly related to SMI without or with accounting for age, for either reader.

Similarly, to overall survival, event-free survival was greatest for patients with higher values ($Z \geq 1$) one standard deviation or greater above the mean for SMD but with no apparent relationship for SMI (Figure 4). At 2 years, overall survival was 12.5%, 55.4%, and 90%, respectively, for SMD one standard deviation or less below the mean, SMD within a standard deviation of the mean, and SMD one standard deviation or higher above the mean. At 5 years, overall survival also showed a progressive relationship of increasing survival: 12.5%, 46.4%, and 80%, with higher standardized deviations of SMD.

Intra-rater Reliability

Both readers had high intra-class correlation, indicating excellent reliability. For Reader 1 using PACS, intra-class correlation was 0.9 for measures of SMD and SMI. For Reader 2 using OsiriX, intra-class correlation was above 0.9 for all measures of SMD. SMI was less reliable on OsiriX, with intra-class correlation ranging from 0.47–0.94.

DISCUSSION

SMD, a measure of muscle quality, can be reliably determined at the T12 level on staging chest CT scans. Patients with higher SMD, representing decreased muscle adiposity and increased muscle quality, had increased overall and event-free survival compared to patients with lower SMD. This relationship persisted with inclusion of age for overall survival. For event-free survival, the estimated mean effect of SMD also was similar after controlling for age although the relationship did not remain statistically significant. This change in significance may be due to the relatively small sample size with limited statistical power. These results suggest an association between survival and muscle quality at the T12 level on chest CT and support the work of Veld et al [13] who reported psoas SMD on abdominal CT (L4 level) was associated with mortality in fully adjusted models. A larger series would be necessary to determine the relative contributions of age and muscle adiposity as measured by SMD.

SMI, as a measure of paravertebral muscle quantity at the T12 level, was not significantly associated with overall or event-free survival. Despite recent findings by Hendrickson et al that SMI is an independent predictor of 1-year mortality in patients with sarcomas in the extremities, our results are consistent with previous results reported by Wilson et al where SMI was not a predictor of overall survival ($p = 0.746$), after controlling for sex ($p = 0.712$) in a Cox proportional hazard model [11]. Unlike Wilson et al and our current study, Hendrickson et al included both bone and soft tissue sarcomas in their analysis, which may result in greater heterogeneity in the cohort due to disease and treatment differences [12]. Unlike both prior studies that evaluated the psoas muscle on abdominal CTs at the L3 level, our study assessed the paravertebral muscle on chest CTs at the T12 level. Although skeletal muscles are most commonly evaluated by CT at the L3 level, measurements at T10-L5 have been validated [19, 22]. Importantly, paravertebral muscle density and size can now be measured automatically with machine learning algorithms in large cohorts [23], such as in the National Lung Screening Trial [24].

Inherent limitations of our study include the small sample size which is reflective of the rarity of STS as well as our restriction to Grade 2 and 3 disease. The non-significant findings of SMI's influence on overall survival in patients with STS in our study and Wilson's may be due to the lack of power. Moreover, our study is a single-centered, retrospective evaluation of STS with significant histological heterogeneity. Insufficient follow-up data and the relatively small sample size further limited our statistical analysis. In line with previous literature where STS stage was important in survival outcomes of STS, univariate analysis demonstrated STS stage was significantly associated with overall and event-free survival, confirming the validity of our patient data [25–26]. Multi-variate modeling was not performed due to limitations of the cohort size. However, age was adjusted for due to the expected confounding between age and muscle metrics [10].

Strengths of our study include the use of two image analysis programs by two trained independent readers demonstrating high intra-reader reliability. Furthermore, compared to most prognostic tumor biomarkers such as tumor grading, staging, and histology that account for tumor aggressiveness, proxy measures of muscle by SMD and SMI may reflect both tumor and patient characteristics [6]. Sarcopenia can develop secondarily from tumor-induced systemic inflammation or metabolic disturbances representing an intrinsically weakened, functionally impaired patient condition. These metabolic disturbances have been demonstrated in multiple studies with various forms of cancer using a prognostic value of the CRP/Alb ratio [6, 27–28]. Due to its ability to assess both tumor and patient status, CT-derived muscle metrics can serve as opportunistic prognostic biomarkers of survival outcomes in STS. At the same time, skeletal muscle represents a potentially modifiable risk factor, regardless of the cause of muscle depletion (e.g., age-related sarcopenia or cancer-related cachexia). Diagnosis using opportunistic CT could allow interventions earlier in the disease course, when the window of anabolic potential is open [29], which may help improve sarcopenia and thus outcomes in patients with STS. Currently, there are 116 trials in progress evaluating nutrition, supplements, exercise (e.g., pre-habilitation), diet, and pharmaceuticals for sarcopenia (listed at clinicaltrials.gov) [30].

Discrete categorical values for muscle metrics in STS staging chest CTs could be useful in screening patients, thereby identifying those patients at risk of poor prognosis for possible intervention and adjustments to treatment including nutritional support and adjuvant therapies. While this study found survival to generally increase with increasing SMD values, given the small sample size and inherent patient variability, a considerably larger sample size would be needed to identify specific thresholds for clinical application.

CONCLUSIONS

Our study is the first to show that muscle quality (i.e., SMD) on chest CTs obtained for routine staging is a significant predictor of survival in patients with STS. Furthermore, these measurements were reproducible between different readers and different image analysis platforms. We did not find any significant association between paravertebral muscle quantity (i.e., SMI) at T12 and survival in patients with STS, mirroring the results of previous studies evaluating psoas SMI at L3 on CTs of the abdomen [11]. Future studies are needed to confirm our findings that SMD on routine chest CT scans is an independent predictor of mortality in STS and investigate clinically relevant cut-off values that may aid in risk stratification (e.g., predict treatment failure during adjuvant therapy), contribute to personalized medical management, and ultimately optimize patient outcomes.

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ABBREVIATIONS

STS	Soft Tissue Sarcoma
SMD	Skeletal Muscle Density in Hounsfield Units (HU) as a measure of muscle quality
SMI	Skeletal Muscle Index in (cm ² /m ²) as a measure of muscle quantity adjusted for patient height
FNCLCC	French Federation of Cancer Centers
AJCC	American Joint Committee on Cancer
CI	Confidence Interval
CT	Computed Tomography
HR	Hazard Ratio
AWD	Alive with Disease

DOD	Died of Disease
NED	No Evidence of Disease

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Synopsis:

Our study evaluates muscle metrics, measured at the T12 vertebral level on staging chest CT scans, as prognostic indicators of overall and event-free survival in patients with soft tissue sarcomas.

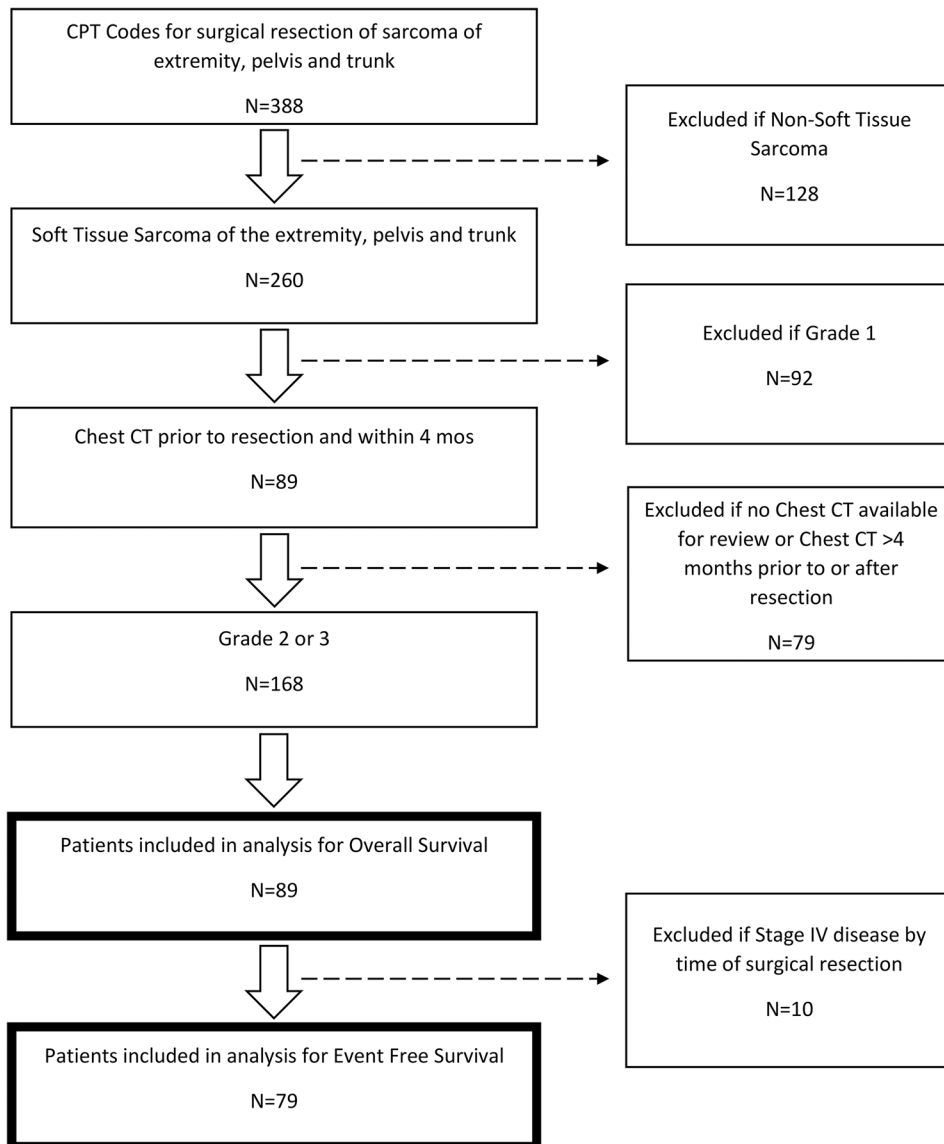


Figure 1. CONSORT diagram depicting patient exclusion criteria frequencies and final cohort size for overall survival and event free survival.

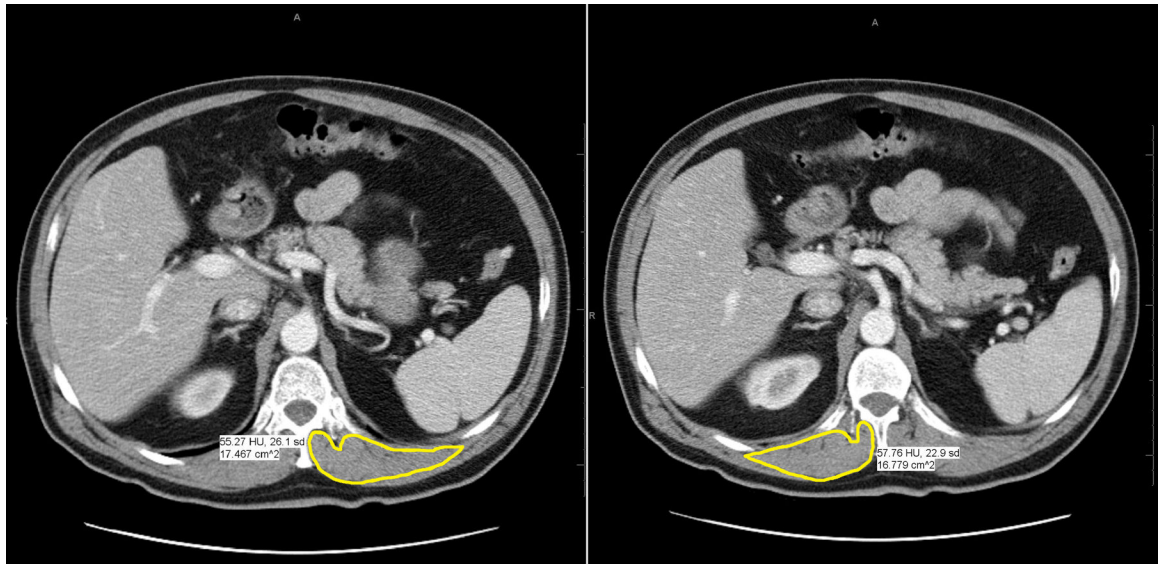


Figure 2. CT images of left and right paravertebral muscle density (HU) and cross-sectional area (cm²) using PACS viewing software.

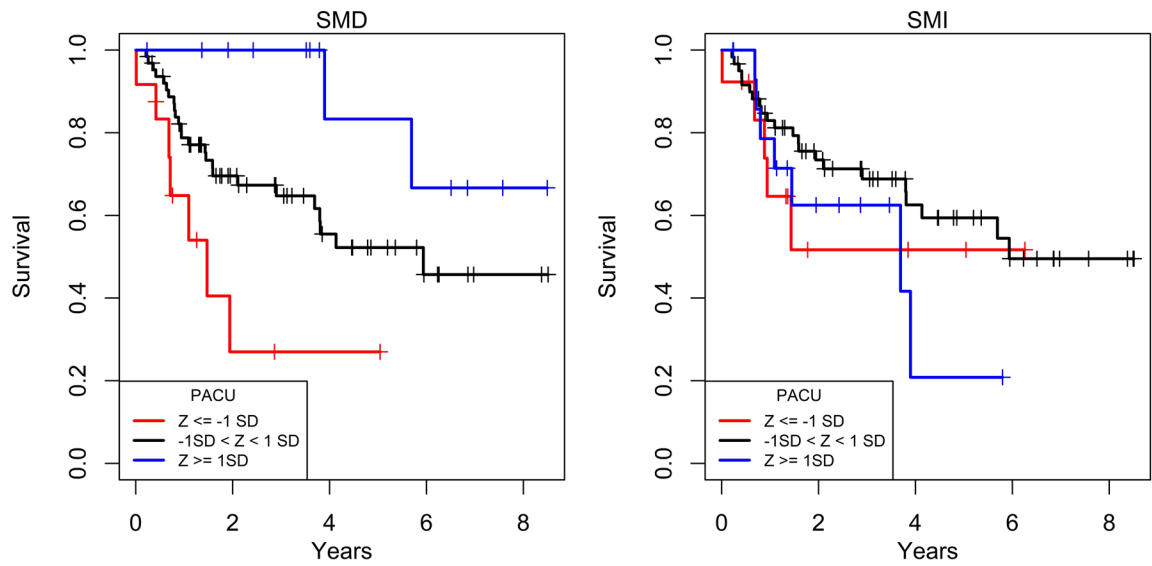


Figure 3. Kaplan-Meier curves of overall survival relative to PACS by standardized deviations of SMD and SMI. Overall survival progressively increased with higher standardized deviation categories above the mean SMD but did not change in association with standardized deviation categories of SMI.

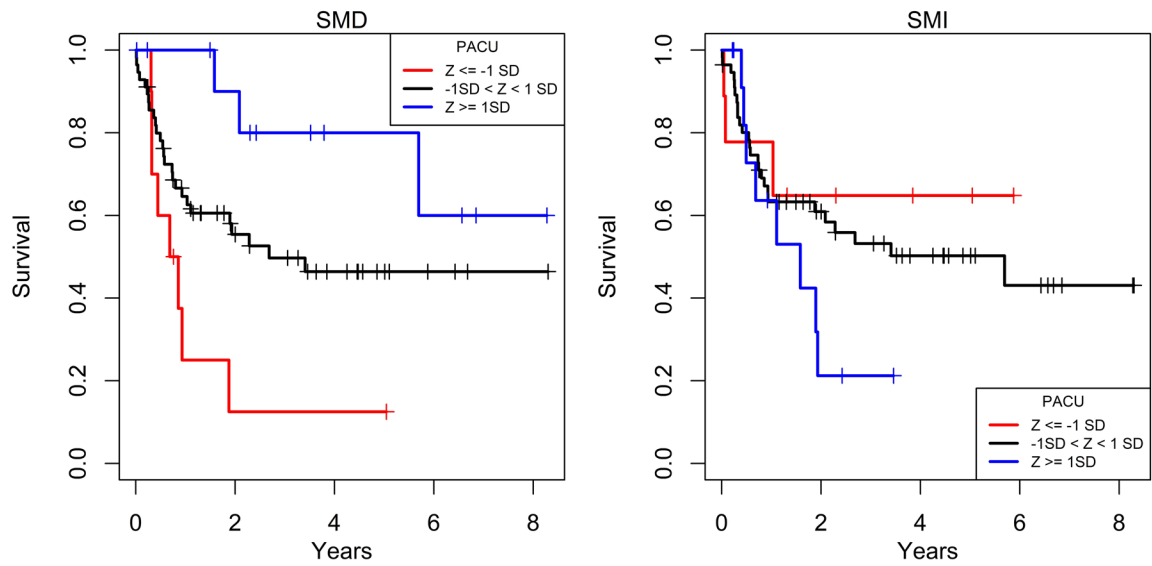


Figure 4. Kaplan-Meier curves of event-free survival relative to PACU by standardized deviations of SMD and SMI. Event-free survival progressively increased with higher standardized deviation categories with SMD but did not change in association with standardized deviation categories of SMI.

Table I.

Patient Demographics

	AWD	DOD	NED
Age			
<i>Average</i>	52.9 ± 20.3	61.9 ± 14.1	58.2 ± 21.9
Sex			
<i>Female</i>	3 (23.1%)	14 (41.2%)	19 (45.2%)
<i>Male</i>	10 (76.9%)	20 (58.8%)	23 (54.8%)
Ethnicity			
<i>African American</i>	3 (23.1%)	14 (41.2%)	19 (45.2%)
<i>Asian</i>	10 (76.9%)	20 (58.8%)	23 (54.8%)
<i>Caucasian</i>	6 (46.2%)	21 (61.8%)	31 (73.8%)
<i>Hispanic or Latino</i>	3 (23.1%)	4 (8.8%)	5 (11.9%)
<i>Other</i>	2 (15.4%)	5 (14.7%)	3 (7.1%)
Charlson-Deyo Score			
<i>0</i>	7 (53.8%)	23 (67.6%)	27 (64.3%)
<i>1</i>	5 (38.5%)	7 (20.6%)	8 (19%)
<i>2</i>	1 (7.7%)	4 (11.8%)	7 (16.7%)
Tumor Location			
<i>Extremity</i>	12 (92.3%)	26 (76.5%)	36 (85.7%)
<i>Trunk</i>	1 (7.7%)	8 (23.5%)	6 (14.3%)
Tumor Size			
<i>10 cm in greatest dimension</i>	4 (30.8%)	19 (55.9%)	32 (76.2%)
<i>>10 cm in greatest dimension</i>	9 (69.2%)	15 (44.1%)	10 (23.8%)
Tumor Grade			
<i>2</i>	2 (15.4%)	2 (5.9%)	5 (11.9%)
<i>3</i>	11 (84.6%)	32 (94.1%)	37 (88.1%)
Tumor Stage			
<i>II</i>	1 (7.7%)	3 (8.8%)	16 (38.1%)
<i>IIIA</i>	3 (23.1%)	15 (44.1%)	16 (38.1%)
<i>IIIB</i>	6 (46.2%)	10 (29.4%)	10 (23.8%)
<i>IV</i>	3 (23.1%)	6 (17.6%)	0 (0%)
Surgical Margins			
<i>Negative</i>	10 (76.9%)	29 (85.3%)	39 (92.9%)
<i>Positive</i>	3 (23.1%)	5 (14.7%)	3 (7.1%)
Tumor Pre-Op Treatment			
<i>Both</i>	2 (15.4%)	8 (23.5%)	8 (19%)
<i>Chemo</i>	2 (15.4%)	1 (2.9%)	2 (4.8%)
<i>None</i>	5 (38.5%)	11 (32.4%)	15 (35.7%)
<i>RT</i>	4 (30.8%)	14 (41.2%)	17 (40.5%)

	AWD	DOD	NED
Tumor Post-Op Treatment			
<i>Both</i>	3 (23.1%)	4 (11.8%)	2 (4.8%)
<i>Chemo</i>	5 (38.5%)	13 (38.2%)	4 (9.5%)
<i>None</i>	3 (23.1%)	11 (32.4%)	31 (73.8%)
<i>RT</i>	2 (15.4%)	6 (17.6%)	5 (11.9%)
Length of Follow-Up			
<i>Average</i>	31.96 ± 19.23	23.53 ± 18.63	50.21 ± 29.13
PACS SMD (HU)			
<i>Average</i>	37.3±16.6	34.2±13.2	41.2±13.2
PACS SMI (cm²/m²)			
<i>Average</i>	4.9±1.5	4.5±1.3	4.4±1.3
OsiriX SMD (HU)			
<i>Average</i>	39.4 ± 15.9	36.9 ± 12.9	43.7 ± 12.8
OsiriX SMI (cm²/m²)			
<i>Average</i>	3.9 ± 1.2	3.9 ± 2.0	3.5± 1.2

Table II.

Association between patient and tumor characteristics with Overall Survival and Event Free Survival.

	Overall Survival	Event-free Survival
Variable	P-value	P-value
<i>Age</i>	0.060 ^b	0.03 ^b
<i>Sex (M vs. F)</i>	0.80 ^a	0.30 ^a
<i>Ethnicity (White vs. other)</i>	0.40 ^a	0.80 ^a
<i>Charlson-Deyo (0 vs. > 0)</i>	0.70 ^a	0.30 ^a
<i>Location (Extremity vs. Trunk/Other)</i>	0.70 ^a	0.50 ^a
<i>Size (≤ 10 cm vs. >10 cm)</i>	0.080 ^a	0.40 ^a
<i>Grade (2 vs. 3)</i>	0.40 ^a	0.30 ^a
<i>Stage (II, IIIa, IIIb IV)</i>	0.008 ^a	0.20 ^a
<i>Margins (- vs. +)</i>	0.50 ^a	0.20 ^a

^aLog rank test^bProportional hazard model

Table III.

Hazard ratios [95% confidence limits] and p-values for one standard deviation change in sarcopenia metric from proportional hazard model analysis of the effect of muscle metrics on overall survival with (Age-adjusted) and without (Univariate) adjusting for age

	SMD		SMI	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Univariate				
PACS	0.61 [0.43, 0.86]	0.005	1.09 [0.74, 1.6]	0.673
OsiriX	0.61 [0.43, 0.86]	0.005	1.09 [0.79, 1.5]	0.603
Age-adjusted				
PACS	0.65 [0.42, 0.98]	0.041	1.26 [0.85, 1.88]	0.249
OsiriX	0.64 [0.42, 0.98]	0.038	1.21 [0.89, 1.63]	0.225

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Table IV.

Hazard ratios [95% confidence limits] and p-values for one standard deviation change in sarcopenia metric from proportional hazard model analysis of the effect of muscle metrics on event-free survival with (Age-adjusted) and without (Univariate) adjusting for age.

	SMD		SMI	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Univariate				
PACS	0.68 [0.49, 0.95]	0.024	1.28 [0.89, 1.85]	0.182
OsiriX	0.66 [0.48, 0.92]	0.015	1.13 [0.85, 1.49]	0.404
Age-adjusted				
PACS	0.68 [0.43, 1.07]	0.098	1.35 [0.88, 2.08]	0.165
OsiriX	0.69 [0.45, 1.08]	0.102	1.25 [0.9, 1.74]	0.187